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FACSIMILE COVER SHEET

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SCR

Our Ref: 1171-101

Your Ref: 09/491,982 Date: November 20, 2000 NOV 29, 2000 Received

TO: *Examiner Prasad*

SUBJECT: *PCT IPER*

FIRM: *USPTO*

FACSIMILE NO.: 703-308-8494

FROM: *Len Mitchard*

NUMBER OF PAGES (INCLUDING COVER SHEET):

(IF YOU DO NOT RECEIVE ALL OF THE PAGES OR ENCOUNTER DIFFICULTIES IN TRANSMISSION, PLEASE CONTACT US IMMEDIATELY AT (703-816-4000).

FACSIMILE OPERATOR

ATTACHMENT/S
:

MESSAGE: **Dear Examiner Prasad:**

Attached is a copy of the IPER.

Len Mitchard
[Tel: 703-816-4005; telefax 703-816-4100]

OK

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

HIRONS, Robert G.
Ridout & Maybee
150 Metcalfe Street
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Ottawa, Ontario K2P 1P1
CANADA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year) 23.08.2000

Applicant's or agent's file reference
29210-0026

IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/CA99/00516	19/05/1999	19/05/1998

Applicant
HAMILTON CIVIC HOSPITAL RESEARCH ... et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

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Authorized officer

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Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
29210-0026		
International application No. PCT/CA99/00516	International filing date (day/month/year) 19/05/1999	Priority date (day/month/year) 19/05/1998

International Patent Classification (IPC) or national classification and IPC
A61K38/00

Applicant
HAMILTON CIVIC HOSPITAL RESEARCH ... et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

I ☒ Basis of the report
II ☐ Priority
III ☒ Non establishment of opinion with regard to novelty, inventive step and industrial applicability
IV ☒ Lack of unity of invention
V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
VI ☐ Certain documents cited
VII ☐ Certain defects in the international application
VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29/11/1999	23.08.2000

Name and mailing address of the international preliminary examining authority:
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Authorized officer
Schnack, A

Telephone No. +49 89 2399 8149

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00516

see separate sheet

☐ the description, claims or drawings (*Indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-46, 49.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00516

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-16,18-31	as originally filed			
17	as received on	19/06/2000	with letter of	19/06/2000

Claims, No.:

1-49	as received on	19/06/2000	with letter of	19/06/2000

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages.
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-28, 49.

because:

- ☒ the said international application, or the said claims Nos. 1-28, 49 relate to the following subject matter which does not require an international preliminary examination (*specify*):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00516

V. Reasoned statement under Articl 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-9, 19-27, 29-33, 36, 39, 41, 42
	No:	Claims	1-3, 10-18, 28, 34, 35, 37, 38, 40, 43-46, 49
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-16, 49
Industrial applicability (IA)	Yes:	Claims	29-39, 41-46
	No:	Claims	see seperate sheet

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET International application No. PCT/CA99/00516

Reference is made to the following documents:

D1: J. Exp. Med., vol. 183, 1996. pp. 2581-2591.
D2: WO 96 195 74
D3: WO 96 186 48

Section I
Basis

The applicant has during the procedure, with letter dated 04.04.2000, filed figure sheets 1-14 and page 28A including table 1. It appears to be confirmed by applicants letter of the same date that these figures and table 1 by mistake were not originally filed on 19.05.1999 as the rest of the application pages were. Even though the originally filed pages refer to the figures and the table, (cf. originally filed pages 5-7 and page 28, the last two lines), and even though it is clear that the figures and table is missing from the application as originally filed, it is from those pages not unambiguously derivable what the figures and the table show. Hence, pursuant to Article 34((2)(b), the later submitted figures and the table cannot be considered to be part of the originally filed disclosure. Thus, in view of the offence against Article 34(2)(b), these pages cannot be considered to be a part of the application as originally filed. Consequently also the references to the figures and the table must be deleted or the text at least reformulated so that no reference to figures and tables, which are not part of the application, is present in the application.

Section III
Non-establishment of opinion

Claims 1-28, 40 and 49 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section IV
Non-unity
Remarks under Rule 13(1) PCT:

The subject matter of present claims 47 and 48 cannot be considered to be linked with the subject matter of present claims 1-46 and 49 in a way that fulfils the requirements of Rule 13(1) PCT, the reasons being as follows. applicant claims that the single novel and inventive concept of the present application is a process of increasing bone density in a mammalian patient. However, the common novel and inventive feature of such a process with the subject matter according to present claims 47 and 48 cannot be seen, since these claims relate to the use of certain assays for identifying IL-11 antagonists. Since IL-11 antagonists or IL-11R binding peptides as well as screening methods for detecting these are already known in the prior art, (see e.g. D2, page 14, line 14 - page 17, line 2 and page 27, lines 1-20), no novel and inventive common concept linking the subject matter according to present claims 47 and 48 with the rest of the claims can be seen.

Section V
V.1. Novelty
Remarks under Article 33(2) PCT:

D1 discloses the basis for the present subject matter; namely that the gp130-coupled cytokine IL-11 plays a central role in osteoclast development. Anti-IL-11 antibody inhibits osteoclast formation induced by several osteotropic factors and the gp130 signal, activated by IL-1,1 is stated to be a clearly important pathway of OCL-formation. It is concluded that it is likely that IL-11 induces osteoclast formation by activating gp130 signals via IL-11 receptors present on osteoclasts and that diseases such as rheumatoid arthritis synovium could be caused at least partly by excessive osteoclastic bone resorption. Moreover, murine monoclonal anti-gp130 antibody was used in D1 in order to establish the effect on osteoclast formation and it was found that the antibody inhibited osteoclast formation, (see D1, the abstract and page 2582, col. 1 and pages 2587-2589 "Discussion" and figure 7). Anti-gp130 antibodies are preferred compounds according to the present application. However, D1 only reports on in-vitro studies, for which reason the subject matter according to present claims 1-28 and 49 appears to

fulfil the requirements for novelty in view of D1.

The present application states that some anti-IL-11 antibodies are commercially available, (cf. present page 13, lines 19-28), for which reason the novelty of the subject matter according to present claims 34-44, should be further elucidate din the national/regional phase. However, D1 refers to a study where anti-Il-11 antibody has been used, (see D1, page 2582, 1. col., 2nd paragraph). Thus, it appears that the subject matter of at least present claims 34 and 43 lacks novelty over that disclosure. The document describing the study referred to may be needed in order to establish novelty of the subject matter according to present claims 35-42.

D2 discloses human IL-11R and inhibitors of binding of Il-11 and Il-11R. D2 further discloses compositions comprising antibodies to IL-11R and inhibitor of binding of IL 11 and IL-11R. D2 discloses methods for identifying an inhibitor to the human IL-11 receptor. The substances according to D2 are useful in the treatment of bone loss, e.g. postmenopausal bone loss. (see D2, the abstract, page 6, line 1 - page 7, line 3, page 14, line 14-page 17, line 2, page 22, line 10-14 and the claims). D2 discloses the sequence of IL-11R. It appears that the subject matter of present claims 13, 35 and 37 falls under the sequence of IL-11R disclosed in Do. (see Do, SEQ ID NO: 1 amino acids nos 234-240). It also appears that the subject matter of present claim 38 falls under the sequence of IL-11R disclosed in Do, (see Do, SEQ ID NO: 1, amino acids 214-233). Thus, the subject matter of present claims 1-3, 10-18, 28, 34, 35, 37, 38, 40, 43-46 and 49 appears to lack novelty over the disclosures in Do.

V.2. Inventive step

Remarks under Article 33(3) PCT:

It is known from D1, D2 and D3 that the ligands of IL-11 induce the formation of a receptor complex of which the membrane molecule gp130 is a part, (see D1, the introduction, D2 the, page 9, lines 9-22, D3, the abstract and cf. present application, page 2, lines 7-12). The formation of this complex is thus necessary for signal transduction. Since it is known from D1 and D2 that inhibition of the interaction between Il-11 and its receptor leads to inhibition of osteoclast formation, which in turn is beneficial in the treatment of osteoporosis, because inhibition of osteoclast formation obviously leads to an increase in bone density, it appears to be obvious to make use of

any method of inhibiting the formation of said complex, i.e also administration of transcribable genetic material. Since all present methods of inhibition of this complex formation appears to be known in the art, such general methods cannot be considered to involve an inventive step.

Moreover, D1 also discloses that since both osteoclasts and osteoblasts express IL-11Rα mRNA both are potential targets for IL-11, (see D1, the abstract). Therefore, it does not require inventive skills to investigate to function of IL-11 also on osteoblasts.

Consequently, novel subject matter falling within the scope of present claims 1-46 and 49 appears to lack an inventive step.

It appears, however, that at least some of the specific mutated proteins and peptides according to the present claims could involve an inventive step, since it appears that the active IL-11 and gp130 binding sites on the IL-11R are not disclosed in the prior art.

V.3. Industrial Applicability
Remarks under Article 33(4) PCT:

For the assessment of the present claims 1-28, 40 and 49 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII
Remarks under Article 5 and 6 PCT:

The present claims contains many expressions and terms, which are considered to be unclear:

Present claim 1 aims at defining its scope through a desired result to be achieved:

"inhibiting the formation of a tertiary complex of IL-11, IL-11R and gp130". The claim does not contain any technical or structural features, which teach the skilled man how to accomplish such an inhibition. Thus, the claim is considered to be unclear and to imply an undue burden on the skilled man seeking to establish the scope of the claim. He would have to conduct in-vivo studies to establish, which substances fall within the scope of the claim, since the applicant alleges that in-vitro studies do not suffice to establish in-vivo efficacy.

A "mutant IL-11R" according to present claims 4, 5 and 29 is considered to be unclear, because it is not clear what the mutation should be. Only claiming a "mutant" form is considered to be an insufficient disclosure for several reasons: not all mutant IL-11R would solve the problem; i.e. not all IL-11R would inhibit the formation of the tertiary complex according to claim 1. The skilled man must conduct cumbersome studies to determine which mutations of the IL-11R do solve the problem, which is considered to be an undue burden on the skilled man.

The difference between "an anti IL-11 antibody" according to present claim 10, "an IL-11 binding peptide" according to present claim 11 and "an IL-11 antagonist" according to present claim 15 is not clear. It appears that all such substances are characterized through the ability to bind to IL-11 and thus interfere with the formation of the tertiary complex. Thus, no difference can be seen and the expressions are consequently considered to be unclear. Thus, also claim 34 is unclear.

The same objection applies for the subject matter according to present claims 16-18 and 44-46, which claims concern substances, which bind to the IL-11 receptor and thus interfere with the formation of the tertiary complex

Present claim 14 is unclear, because the term "a small molecule" is indefinite and unclear.

Present claim 19 is also unclear, because the term "transcribable genetic material which causes inhibition of the formation of ..." is also considered to be a claim, which aims at defining its scope through a desired result to be achieved, rather than through technical features leading to this result. It would imply an undue burden on the skilled man seeking to establish the scope of the claim to determine which genetic material is

in fact covered by the claims. Especially, because it appears that he would have to conduct in-vivo studies, since applicant claims that in-vitro result may not suffice.

Moreover, the term "antagonist" is usually used to mean a receptor antagonist. In the present context it is however not quite clear what is meant by "IL-11 antagonist", (e.g. claim 15), since it does not appear to concern the receptor antagonist.